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THE EFFECT OF IMMUNOSUPPRESSIVE DRUGS ON QUALITY OF LIFE AFTER RENAL TRANSPLANTATION

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This prospective, randomized study investigates the effect of two immunosuppressive treatment regimens on quality of life after renal transplantation. At 3 months after transplantation, patients treated with cyclosporine (CsA) and prednisone (Pred) were allocated to either withdrawal of Pred (n=60) or to conversion of CsA to azathioprine (Aza) (Aza-Pred, n=60). Quality of life was evaluated just before randomization, and at 6 and 12 months after transplantation using the Sickness Impact Profile (SIP), the Affect Balance Scale (ABS), the Center for Epidemiological Studies Depression Scale (CES-D), measures of satisfaction with several domains of life experience, and a population-specific physical symptoms questionnaire. In both groups, the overall SIP score as well as the scores on its physical and psychosocial dimensions improved continuously after transplantation, reaching levels that are comparable to those found in the general population. The occurrence of acute or chronic rejection had a significantly negative effect on SIP and CES-D scores. Intention-to-treat analysis showed no differences between groups for scores on SIP, ABS, CES-D, and satisfaction measures. Exclusion of 41 patients who did not strictly adhere to their originally designated therapy showed a tendency for better psychosocial SIP scores in CsA patients (P=0.05), which mainly resulted from a difference on the category of social interaction (P=0.01). This difference occurred despite a similar rejection rate and worse renal function in CsA-treated patients. Shortly after steroid withdrawal, a high proportion of CsA patients complained of stiff or painful muscles (CsA: 74%, Aza-Pred: 36%; P=0.002). Our data indicate that if successfully completed, CsA monotherapy from 3 months after transplantation may lead to a higher degree of psychosocial well-being as compared with conversion from CsA-Pred to Aza-Pred. It seems likely that this advantage is related to the withdrawal of Pred.

One of the primary goals of renal transplantation is to improve the quality of life of the patient with end-stage renal disease. Traditional research efforts, however, have mainly been directed at prolonging patient and graft survival. These survival rates have improved considerably during the last decades and any further progress will be hard to achieve. Therefore, it is not surprising that the quality of life of the patients with prolonged survival is receiving a growing amount of attention (*1*, *2*).

The type of immunosuppressive drug therapy is one of the factors that determine the quality of life after renal transplantation. First, an effective immunosuppressive regimen, leading to prolonged patient and graft survival, is a prerequisite to reach an optimal level of quality of life. Besides, treatment schedules may act more directly on quality of life by means of their adverse effects, which will differ according to the drugs that are used. Patients' psychosocial functioning, which they will partly attribute to prescribed medication, will in turn have influence on the compliance with the therapeutic regimen (*3*). Eventually, compliance is one of the main determinants of long-term graft survival (*4–7*).

Our aim was to investigate the impact of the currently most frequently used immunosuppressive drugs on changes in quality of life during the first year after renal transplantation. Health-related quality of life was therefore measured in participants in a randomized prospective trial comparing cyclosporine (CsA)* monotherapy with the combination of azathioprine (Aza) and prednisone (Pred) from 3 months after renal transplantation.

PATIENTS AND METHODS

Patient population. From July 1989 to June 1992, all adult patients who underwent a first or second cadaveric renal transplantation at our institution were invited to take part in this study. Patients were excluded when they fulfilled one or more of the following exclusion criteria: age above 65 years, history of psychiatric disease or alcohol abuse, history of malignancy, poor knowledge of Dutch language, signs of active hepatitis or carriage of hepatitis B surface antigen, hemolytic uremic syndrome as original kidney disease, use of anti-epileptic drugs, and allergy to Aza. After surgery, patients were treated with CsA and Pred for 3 months. Afterward, they were randomly allocated to CsA monotherapy or to the combination therapy of Aza and Pred. At 3 months after transplantation, 59 of the 186 patients who initially entered the study could not be randomized to a treatment arms for one of the following reasons: patient death or graft loss in the first 3 months after transplantation (n=39), loss of patient to follow-up (n=1), contraindication for CsA by clinical judgment (usually because of signs of CsA nephrotoxicity; n=16), use of Aza contraindicated because of bone marrow depression (n=2), and use of Pred contraindicated because of severe osteoporosis (n=1).

Study protocol. CsA was given intravenously (3 mg/kg/day) for the first 3 days after surgery followed by 12 mg/kg/day in 2 divided oral doses during the first month. This dosage was gradually reduced to 4 mg/kg/day at 3 months after transplantation. The dosage was adjusted to maintain CsA trough blood levels between 200 and 400 ng/ml. Prednisolone was given at a dose of 100 mg/day i.v. during the first 2 days after surgery, followed by an oral Pred dosage of 25 mg/day during the remainder of the first month and 20 mg/day

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* Abbreviations: ABS, Affect Balance Scale; ATG, antithymocyte globulin; Aza, azathioprine; CES-D, Center of Epidemiological Studies Depression Scale; CsA, cyclosporine; Pred, prednisone; SIP, Sickness Impact Profile.

during the second and third month after transplantation. In patients who were randomized to receive CsA monotherapy, CsA was continued in the same dosage, with adjustments to reach trough blood levels between 100 and 200 ng/ml. The daily Pred dosage was reduced by 5 mg every 2 weeks, resulting in CsA monotherapy after 6 weeks. In patients allocated to Aza-Pred therapy, CsA was replaced without overlap by Aza at a dosage of 3 mg/kg. Their Pred dosage was temporarily increased from 20 to 25 mg/day and reduced by 5 mg every 2 weeks until a maintenance dose of 10 mg/day was reached. In the CsA group, Pred was restarted if more than 1 acute rejection or chronic vascular rejection occurred after randomization. The same conditions led to replacement of Aza by CsA in the Aza-Pred group. In case of severe and persistent side effects, attributable to one of the drugs, patients were put on the alternative treatment regimen.

During the first 3 months after transplantation, acute rejection episodes were treated with methylprednisolone (1 g i.v. on 3 consecutive days) or antithymocyte globulin (ATG; RIVM Bilthoven, The Netherlands; 200 mg i.v. on alternate days for 10 days). An oral course of high-dose Pred (initial dosage 200 mg/day tapering to 25 mg/day in 12 days) was given after failure of one or both of these treatments.

From 3 months after transplantation (i.e., after randomization), acute rejections were treated primarily with ATG in all cases. High-dose Pred courses were given in case of failure of ATG, bone marrow suppression, or previous treatment with ATG for rejection.

Hypertension, defined as diastolic blood pressure above 95 mmHg on 3 consecutive occasions, was treated in a standard way using a β-blocker (atenolol), followed by the successive addition of a calcium antagonist (nifedipine) and a diuretic (chlorthalidone) when necessary.

Quality of life measurements (see below) were carried out at 3 months (i.e., before randomization) as well as at 6 and 12 months after transplantation. Body weight and blood pressure as well as results from routine clinical chemistry were recorded at regular intervals as part of the usual posttransplant patient evaluation. Body mass (Quetelet) index was calculated as weight in kg divided by the square of the height in meters. Creatinine clearance was estimated with the formula given by Cockcroft and Gault (*8*).

The study was approved by the Hospital Ethics Committee and all patients gave written informed consent.

Quality of life assessment. Questionnaires were administered by a single trained interviewer who was not aware of medical data of the patients, including their type of treatment. The questionnaire consisted of both generic measures and of questions rather specific for the population of renal transplant patients. The generic measures comprised the Sickness Impact Profile (SIP), the Affect Balance Scale (ABS), the Center of Epidemiological Studies Depression Scale (CES-D), and questions on satisfaction with several domains of life experience. The SIP measures sickness-related behavioral dysfunction and contains 136 items that can be divided into 12 categories (*9*). Three categories can be aggregated into a physical dimension (ambulation, mobility, and body care and movement), 4 categories make up a psychosocial dimension (social interaction, alertness behavior, communication, and emotional behavior), and 5 categories are independent (eating, work, home management, sleep and rest, and recreation and pastimes). Total scores and scores on the various categories and dimensions are expressed on a scale of 0 to 100, with higher scores denoting worse state. The Dutch version of the SIP that we used has been validated (*10*). The ABS contains 10 questions on positive and negative feelings during the past few weeks (*11*). Scores on the ABS can vary from 1 to 9, with higher scores indicating a more favorable grade of well-being. The CES-D is another standardized measure of affect. It is composed of 20 items that result in a score which increases along with a more depressive state from 0 to 60 (*12*). In addition to these composite scales, the questionnaire asked for overall life satisfaction and for satisfaction with 4 domains of life experience, derived from the study of Campbell et al. (*13*). We added 2 items questioning satisfaction with sexual activities and with the renal transplantation. The complete list of domain satisfaction measures is given in Appendix A. Finally, the questionnaire contained a set of physical symptoms, a number of them being rather specific for the population of renal transplant patients (Appendix B). Most of these items were gathered from various other studies. Retesting of validity and responsiveness of this disease-specific questionnaire was not considered necessary (*14*).

Statistical analysis. All data were analyzed with the SAS system (SAS Institute Inc., Cary, NC). Because the majority of data were not normally distributed, data are given as medians, with interquartile range in brackets. Unpaired comparisons of numerical data between 2 groups at different time points were carried out with Wilcoxon's rank sum test. Proportions were compared with chi-square analysis using continuity correction. Paired comparisons of numerical and ordinal data within 1 group were performed with Wilcoxon's signed rank test. Simple correlations were assessed by calculating Spearman's correlation coefficient. A P-value smaller than 0.05 was considered statistically significant.

RESULTS

Full evaluation of the data was not possible in 7 of the 127 patients who were allocated to the treatment groups. Two patients (1 in each treatment group) died between 3 and 12 months after transplantation. Two patients (both in the CsA group) were not able to respond to the questionnaire at 6 months after transplantation because of severe illness. Two more patients (1 in each group) discontinued their participation. Finally, in 1 case (Aza-Pred group), the interviewer judged the answers as highly unreliable.

The demographic and clinical characteristics of the remaining 120 patients are shown in Table 1. There were no significant differences between the treatment groups.

Intention-to-treat analysis. Graft loss occurred once in each group between 3 and 6 months after transplantation. To perform an intention-to-treat analysis, these patients were not excluded and they completed the questionnaires while having returned to hemodialysis. The main clinical results of the transplantation are given in Table 2. As expected, renal function improved after conversion from CsA to Aza in the Aza-Pred group. This resulted in a significant difference between groups at 12 months after transplantation. The number of patients with 1 or more acute rejection episodes after randomization (i.e., between 3 and 12 months after transplantation) was 25 (42%) in the CsA group and 16 (27%) in the Aza-Pred group (NS). Chronic rejection was observed in 15 patients (CsA: 10, Aza-Pred: 5; NS) and was only twice not preceded by any acute rejection episode. None of the other parameters that may influence quality of life showed a significant difference between groups. The time course of scores on the SIP, ABS, and CES-D is given in Table 3. A continuous, significant improvement of SIP scores took place between 3 and 12 months after transplantation in both groups. Neither the actual values nor the degree of improvement of any score differed significantly between treatment groups. Acute rejection, chronic rejection, or both were diagnosed in 43 patients between 3 and 12 months after transplantation. Their quality of life during this interval (i.e., at 6 months after transplantation) appeared worse than in nonrejecting patients (Table 4). In the whole group, there was a negative correlation between creatinine clearance and total SIP score (at 3 months $R=-0.41$, $P<0.001$; at 6 months $R=-0.21$, $P=0.02$; at 12 months $R=-0.24$, $P=0.009$). After exclusion of patients who experienced acute or chronic rejection, this

TABLE 1. Characteristics of patients who were treated with CsA monotherapy or Aza and Pred from 3 months after renal transplantation[a]

	All patients (n=120)	CsA (n=60)	Aza-Pred (n=60)
Sex (M/F)	76/44	38/22	38/22
Age (yr)	43(29–53)	43(32–53)	42(28–54)
First/second Tx	98/22	48/12	50/10
Time on dialysis (mo)	23(13–38)	25(12–43)	23(14–38)
Diabetes mellitus	1	1	0
Marital status			
Unmarried, living alone	31	12	19
Married/living together	83	43	40
Widowed	3	2	1
Divorced	3	3	0
Living situation			
Alone	10	4	6
Living with partner/spouse only	38	19	19
Living in a family	60	31	29
Otherwise	12	6	6
Highest level of education			
Basic school	14	5	9
Lower vocational training	45	24	21
Higher vocational training	23	10	13
Lower general secondary education	16	11	5
Higher general secondary education	8	3	5
College	14	7	7
Salaried position	34	18	16

[a] Numerical data are given as medians with interquartile ranges.

TABLE 2. Clinical results at 3 months (before randomization) and 12 months after renal transplantation in patients allocated to CsA monotherapy (n=60) or treatment with Aza and Pred (n=60)

	3 Months		12 Months	
	CsA	Aza-Pred	CsA	Aza-Pred
	numbers (%)			
At least 1 acute rejection	16 (27)	16 (27)	34[a] (57)	29[a] (48)
Chronic rejection	—	—	10 (17)	5 (8)
Antihypertensive therapy	44 (73)	44 (73)	39 (65)	39 (65)
	medians (interquartile ranges)			
Body mass index (kg/m^2)	23.7 (21.3–25.6)	23.3 (21.5–25.8)	25.5[b] (22.6–27.1)	25.0[b] (22.0–27.7)
Weight gain after Tx (%)	3.3 (−0.3–9.2)	4.3 (−0.1–7.7)	10.0[b] (3.7–16.9)	8.6[b] (4.1–12.8)
Creatinine clearance (ml/min)	57 (40–69)	52 (42–66)	53 (43–67)	64[b,c] (53–84)
Hemoglobin (mmol/L)	7.2 (6.3–7.7)	7.0 (6.7–7.8)	8.1[b] (7.3–8.8)	8.1[b] (7.3–8.6)

[a] Including rejections that occurred during the first 3 months.
[b] $P<0.001$ for difference with values of the same treatment group at 3 months after transplantation.
[c] $P<0.001$ for difference with CsA group.

correlation remained significant at 3 months ($R=-0.37$, $P<0.001$), but had disappeared at 6 and 12 months after transplantation.

Per-protocol analysis. In 39 patients, the initially assigned treatment had to be changed for a variety of reasons. Pred was added to CsA in 7 patients because of the occurrence of more than 1 acute rejection or chronic rejection episode after steroid withdrawal. In another 6 patients, steroid withdrawal was not completed for a variety of reasons. CsA was replaced by Aza in 12 cases, all but once because of CsA-induced renal dysfunction. In 2 patients, Aza was replaced by CsA because the patients had a second acute rejection episode after prior conversion from CsA to Aza. Bone marrow depression and liver function disturbances prompted switching from Aza to CsA in 8 and 4 additional patients, respectively. After exclusion of both this group of 39 patients and the 2 patients with graft loss, 79 patients (CsA: n=34, Aza-Pred: n=45) remained available for per-protocol analysis.

The clinical results of the transplantation in this subgroup of patients are given in Table 5. There was no significant difference between treatment regimens in the incidence of acute rejection episodes after randomization (CsA: 10/34 [29%], Aza-Pred: 9/45 [20%]). Regarding quality of life measures, the treatment groups did not differ significantly in actual values at any time point nor in changes over time (Table 6). Nevertheless, there was a trend toward a persistently better score on the psychosocial dimension of the SIP in the CsA monotherapy group. Of the 4 categories that make

TABLE 3. Scores on SIP, ABS, and CES-D at 3, 6, and 12 months after renal transplantation in patients allocated to CsA monotherapy (n=60) or treatment with Aza and Pred (n=60)[a]

	3 Months		6 Months		12 Months	
	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred
SIP						
Total[b]	9.1 (5.5–16.4)	8.7 (3.6–16.5)	5.8[c] (3.7–11.4)	5.3[d] (2.1–14.4)	3.8[c] (1.3–6.5)	3.5[c] (0.5–10.4)
Physical[b]	5.7 (1.5–12.9)	4.1 (1.0–13.9)	1.9[d] (0–10.1)	3.6[e] (0–10.7)	0.8[c] (0–4.4)	1.2[c] (0–6.7)
Psychosocial[b]	4.5 (1.6–14.7)	4.3 (1.9–14.4)	1.9[d] (0–6.9)	4.8 (0–12.3)	1.3[c] (0–4.0)	3.1[c] (0–9.7)
ABS	7 (6–8)	6 (5–8)	7 (5.5–8)	7 (5–8)	7.5 (6–8.5)	7 (5.5–8)
CES-D[b]	2 (0.5–7)	2 (0–6)	2.5 (1–6)	2.5 (0–9)	1[e] (0–4)	1 (0–5.5)

[a] Data are given as medians with interquartile ranges.
[b] Lower scores on these indexes indicate better quality of life.
[c] $P<0.001$ for difference with values of the same treatment group at 3 months after transplantation.
[d] $P<0.01$ for difference with values of the same treatment group at 3 months after transplantation.
[e] $P<0.05$ for difference with values of the same treatment group at 3 months after transplantation.

TABLE 4. Scores on SIP, ABS, and CES-D at 3, 6, and 12 months after renal transplantation in patients with (n=43) and without (n=77) diagnosis of acute or chronic rejection between 3 and 12 months after transplantation, irrespective of treatment group[a]

	Acute/chronic rejection 3–12 mo					
	3 Months		6 Months		12 Months	
	Yes	No	Yes	No	Yes	No
SIP						
Total[b]	9.5 (4.5–16.0)	8.7 (4.8–16.4)	8.7 (3.5–14.7)	4.4[c,d] (2.0–10.7)	4.0[e] (1.8–11.0)	3.5[c,d] (0.4–6.8)
Physical[b]	5.9 (2.2–14.4)	3.8 (0.8–12.3)	5.2 (0–13.4)	1.2[c,d] (0–9.1)	1.5[f] (0–10.2)	0.8[d] (0–3.9)
Psychosocial[b]	4.2 (1.4–14.9)	4.6 (1.9–13.9)	4.2 (0–12.4)	1.9[e] (0–8.1)	3.3[f] (0–8.3)	1.3[d] (0–5.1)
ABS	7 (6–8)	7 (5–8)	7 (6–8)	7 (5–8)	7 (5–8)	7[f] (6–9)
CES-D[b]	2 (0–7)	2 (0–6)	3 (0–7)	2 (0–6)	2 (0–6)	1[c] (0–4)

[a] Data are given as medians with interquartile ranges.
[b] Lower scores on these indexes indicate better quality of life.
[c] $P<0.05$ for difference with patients with rejection.
[d] $P<0.001$ for difference with values of the same group at 3 months after transplantation.
[e] $P<0.01$ for difference with values of the same group at 3 months after transplantation.
[f] $P<0.05$ for difference with values of the same group at 3 months after transplantation.

up this psychosocial dimension, only the social interaction category showed different scores between groups at 6 months (CsA: 0 [0–3.6], Aza-Pred: 3.6 [0–15.2]; $P=0.04$) and 12 months (CsA: 0 [0–3.6], Aza-Pred: 3.5 [0–7.9]; $P=0.01$). None of the 20 individual items within the social interaction category displayed significant differences.

There were no differences in the ratings on the various satisfaction measures. At 1 year after transplantation, only 1 (CsA-treated) patient was slightly dissatisfied with life in general. Also, 1 (Aza-Pred) patient expressed some dissatisfaction with his renal transplantation. On the other hand, 8 patients (CsA: 3/31 [10%], Aza-Pred: 5/37 [14%]; NS) were to some extent (score 5 or higher) dissatisfied with their sex life.

For the evaluation of the incidence of physical symptoms, we interpreted a score of 1 as absence and a score of 2 or higher as presence of the concerning symptom. Table 7 gives the incidence of the 10 most frequent complaints in either group at the various time points, completed by items at which significant differences were observed.

Subgroup analysis for males and females, respectively, did not demonstrate differences between treatment groups on any quality of life index. Analysis of subgroups according to age, with the median age (41 years) as partition, disclosed a significant difference on the psychosocial dimension of the SIP for older patients at 1 year after transplantation (CsA: 0 [0–1.4], Aza-Pred: 2.4 [0–9.3]; $P=0.03$).

Finally, to avoid possible bias by an unequal rejection incidence in both groups, we analyzed the data after exclusion of patients who experienced acute or chronic graft rejection after randomization (CsA: 10/34, Aza-Pred: 10/45). At 6 months after transplantation, CsA-treated patients again tended to have better scores on the psychosocial dimension of the SIP (CsA: 0 [0–4.3], Aza-Pred: 4.9 [0–16.9]; $P=0.06$), with significant differences for its social interaction (CsA: 0

TABLE 5. Clinical results at 3 and 12 months after renal transplantation in patients treated with CsA monotherapy (n=34) or Aza and Pred (n=45)[a]

	3 Months		12 Months	
	CsA	Aza-Pred	CsA	Aza-Pred
		numbers (%)		
At least 1 acute rejection	8 (24)	12 (27)	16[b] (47)	20[b] (44)
Chronic rejection	—	—	0	3 (7)
Antihypertensive therapy	25 (74)	35 (78)	19 (56)	29 (64)
		medians (interquartile ranges)		
Body mass index (kg/m^2)	23.6 (21.9–25.5)	23.2 (21.6–25.6)	25.5[c] (22.8–26.9)	25.0[c] (22.3–27.7)
Weight gain after Tx (%)	2.1 (−0.6–10.0)	4.3 (0.3–9.5)	9.6[c] (4.8–13.3)	9.4[c] (4.1–12.5)
Creatinine clearance (ml/min)	58 (46–71)	51 (42–64)	55 (48–64)	69[c,d] (56–85)
Hemoglobin (mmol/L)	7.3 (6.4–7.8)	7.0 (6.6–7.7)	8.2[c] (7.7–8.8)	8.1[c] (7.5–8.6)

[a] Patients who deviated from their originally assigned treatment were excluded.
[b] Including rejections that occurred during the first 3 months.
[c] $P<0.001$ for difference with values of the same treatment group at 3 months after transplantation.
[d] $P<0.001$ for difference with CsA group.

TABLE 6. Scores on SIP, ABS, and CES-D at 3, 6, and 12 months after renal transplantation in patients treated with CsA monotherapy (n=34) or Aza and Pred (n=45)[a]

	3 Months		6 Months		12 Months	
	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred
SIP						
Total[b]	7.5 (5.3–10.1)	9.4 (4.8–17.7)	5.5[c] (3.5–8.8)	5.2[d] (2.1–12.1)	2.4[d] (0.5–5.4)	3.2[d] (0.4–8.0)
Physical[b]	4.0 (0.8–10.2)	4.7 (1.0–15.1)	1.5 (0–8.6)	1.9[e] (0–9.9)	0[d] (0–3.3)	0.8[d] (0–4.0)
Psychosocial[b]	3.5 (0–9.9)	5.6 (3.0–17.1)	1.4 (0–5.3)	4.9[f] (0–10.1)	0[d] (0–2.8)	3.1[d,g] (0–9.3)
ABS	7 (6–8)	6 (5–8)	7 (6–8)	7 (5–8)	7.5 (6–8)	7[e] (6–8)
CES-D[b]	2 (0–5)	2 (1–7)	2 (1–5)	3 (0–9)	1[e] (0–4)	1 (0–5)

[a] Patients who deviated from their originally assigned treatment were excluded. Data are given as medians with interquartile ranges.
[b] Lower scores on these indexes indicate better quality of life.
[c] $P<0.05$ for difference with values of the same treatment group at 3 months after transplantation.
[d] $P<0.001$ for difference with values of the same treatment group at 3 months after transplantation.
[e] $P<0.01$ for difference with values of the same treatment group at 3 months after transplantation.
[f] $P=0.06$ for difference versus CsA group.
[g] $P=0.05$ for difference versus CsA group.

[0–3.6], Aza-Pred: 3.6 [0–15.4], $P=0.02$) and emotional behavior (CsA: 0 [0–0], Aza-Pred: 0 [0–16.2]; $P=0.04$) categories.

DISCUSSION

Our study population demonstrated an ongoing improvement of quality of life during the first year after transplantation, as measured with the SIP. Previous, cross-sectional studies established a higher quality of life in transplanted patients when compared with patients on hemodialysis or continuous ambulatory peritoneal dialysis (*15–17*), while a few prospective studies have reported a rise in health status after successful transplantation (*18, 19*). Our results indicate that the figures obtained in renal graft recipients depend on the time elapsed after transplantation. Assuming that the transplant procedure itself will have been responsible for a transient drawback in quality of life, it probably takes at least a year to reach the optimal posttransplant level. Although a number of patients at this time still obviously suffered from physical disabilities and complications, the achieved ratings for quality of life were extremely high. Total SIP scores at 1 year after transplantation were comparable to the mean score of 3.4 that was obtained in a sample of the general Dutch population (*10*). The majority of patients (77%) rated 1 or 2 on the 7-point scale for overall life satisfaction. Similar observations were made before in renal (*2, 15–17*) and liver transplant patients (*20, 21*). The favorable scores in these patient groups have been attributed to the feeling of being reborn after transplantation, to the desire to fulfill certain expectations, and to psychological defense mechanisms against fear for rejection and complications (*21*).

During the first year after transplantation, the occurrence of rejection episodes had a clear deteriorating effect on quality of life. Physical complaints related to the rejection process

TABLE 7. Presence of physical complaints at 3, 6, and 12 months after renal transplantation in patients treated with CsA monotherapy (n=34) or Aza and Pred (n=45)[a]

	3 Months		6 Months		12 Months	
	CsA	Aza-Pred	CsA	Aza-Pred	CsA	Aza-Pred
Excessive hair growth	76	64	59[b]	24[c,d]	32[d]	7[c,d]
Swollen face	62	58	12[d]	33[d]	9[d]	20[d]
Need for rest	59	58	65	49	35	42
Feeling tired	59	56	65	44[e]	47	49
Excessive appetite	50	58	6[d]	31[d,f]	18[d]	18[d]
Trembling hands	56	53	18[d]	18[b]	12[d]	4[d]
Too fat	47	44	47	44	44	42
Feeling weak	35	42	35	27	15	22[e]
Stiff or painful muscles	41	42	74[e]	36[c]	35	31
Tingling in hands	26	38	15	16[b]	12[e]	9[d]
Headache	32	27	18	31	18	18
Swollen ankles	24	18	26	16	15	13
Feeling sick	26	24	24	29	15	20
Problems to sleep on	24	33	24	20	9[e]	16
Shortness of breath	21	24	18	31	15	16
Problems to fall asleep	21	24	24	22	21	16
Bruises	24	20	15	29	9	33[f]
Heartburn	15	13	6	20	9	22
Dizziness	9	16	0	20[f]	6	13

[a] Patients who deviated from their originally assigned treatment were excluded. Data are given as percentages.
[b] $P<0.01$ for difference with scores at 3 months after transplantation.
[c] $P<0.01$ for difference with CsA group.
[d] $P<0.001$ for difference with scores at 3 months after transplantation.
[e] $P<0.05$ for difference with scores at 3 months after transplantation.
[f] $P<0.05$ for difference with CsA group.

or worse graft function, side effects of antirejection treatment, and being faced with a serious setback may all have been responsible for the impaired quality of life. Unfortunately, our data do not allow firm conclusions on the degree of reversibility of this phenomenon after successful treatment of acute rejections.

We found no difference in quality of life between our 2 treatment groups. Both groups were similar on demographic variables that have been shown to correlate with total SIP score, such as age, sex, education, and length of time with end-stage renal disease (*17*). Theoretically, any difference should be caused by disparate effects of both treatment regimens on factors such as graft survival, rejection rate, and graft function, or, more directly, by a different array of adverse effects. In our intention-to-treat analysis, especially the latter, possible cause of differences could be obscured by the fact that departure from the originally designated drug therapy occurred in about one third of the patients. Since both treatment regimens were explicitly designed to have no drug in common (CsA vs. the combination of Aza and Pred), we excluded those patients who did not keep to their originally assigned treatment and subsequently performed a per-protocol analysis. Again, no significant differences could be demonstrated in the measured parameters of quality of life. The slightly higher rejection rate and the worse renal function (both associated with a decline in quality of life) in the CsA monotherapy group did not result in a less favorable score on any measure. In fact, there was a tendency for a more beneficial score on the psychosocial dimension of the SIP in these patients, with statistical significance being reached in the older half of the population. A significant difference on the social interaction category appeared to be mainly responsible for this finding. We can only speculate about an explanation for this difference. Lack of the steroid-related appearance may have offered the opportunity for the CsA-treated patients to visit their family and friends more frequently as well as feel themselves more comfortable in contacts with other people. Based on existing knowledge of the effects of corticosteroids on affect and mood ("steroid high"), differences could have been expected on the CES-D and the SIP emotional behavior category. Although improvements on these measures did not differ between groups, scores on the latter item were superior in the CsA monotherapy group after exclusion of patients with acute or chronic rejection.

Ratings on satisfaction measures were quite high in both groups. Notably, the lowest levels of satisfaction were recorded in the sexual life domain. Sexual problems are well recognized in dialysis patients (*22*), but this issue apparently deserves attention after renal transplantation too. For several physical symptoms, a marked improvement between 3 and 12 months after transplantation was observed. The higher incidence of hypertrichosis in the CsA group and the higher incidence of increased appetite and bruises in the Aza-Pred-treated patients were not unexpected. A remarkably high number of CsA-treated patients complained of muscle pain and stiffness during the first few months after withdrawal of steroids. In some of the patients, these complaints were so severe as to urge extended continuation of low doses of Pred, which led to relief of symptoms.

To our knowledge, only once before has quality of life been reported as an outcome variable in a randomized clinical trial in renal transplant patients (*2*). In that study, comparing CsA-Pred with the regimen of antilymphocyte globulin followed by Aza-Pred, quality of life was also assessed at 1 year

after transplantation, although baseline measurements were not performed. Patients on CsA-Pred appeared to fare better on indicators of physical, emotional, and social well-being, but the differences lost statistical significance after correction for the higher number of rejections and infections in the Aza-Pred group. Nonetheless, there remained a tendency for a more favorable score on some measures of emotional well-being in the CsA-Pred patients, who used lower Pred doses than their counterparts in the Aza-Pred group. Our finding of a slightly better score on the psychosocial dimension of the SIP in CsA patients, in spite of a rejection rate which at least equaled that in Aza-Pred patients, adds to this observation. Taken together, these results indicate that lowering the dose or withdrawal of prednisone may improve rather than worsen the quality of life after renal transplantation.

For both the changes over time as well as the effect of rejection on quality of life, the SIP appeared to be our most sensitive measuring instrument. This fits in with the high figures for accuracy and reproducibility that have been reported for this questionnaire in various circumstances (*9*, *23*). Nevertheless, the discriminative capacity of the SIP, and of the ABS and CES-D as well, was impeded by the fairly high quality of life in this population. Therefore, it can be questioned whether the lack of differences between the treatment groups may reflect a type II error, also in connection with the limited size of our patient population. Because of little experience with this type of research in the field of transplantation, we did not have reliable information (e.g., on the expected distribution of the data and meaningful sizes of differences) needed to perform a proper power analysis before the start of the study.

Although the importance of measuring the quality of life is generally appreciated (*1*, *24*), the skeptical reader may ask whether it adds any information to what can be derived from usual clinical judgment and laboratory figures. In this regard, it was instructive that measured parameters of quality of life improved substantially in our CsA-treated patients between 3 and 12 months after transplantation; during this interval, 42% of them experienced one or more acute rejection episodes, and their renal function did not improve at all. Therefore, we believe it is useful to incorporate quality of life measurement in future trials concerning the treatment of organ transplant recipients.

APPENDIX A

Set of Satisfaction Measures

Respondents were asked to rate their satisfaction with each item on a 7-point scale ranging from completely satisfied (1) to completely dissatisfied (7). If an item did not apply for the patient in case, it was skipped.

- In general, how satisfied are you with your life as a whole these days?
- How satisfied are you with the attention and support that you receive from family or surroundings?
- How satisfied are you with your marriage or relationship?
- How satisfied are you with your sexual life?
- How satisfied are you with your daily pursuits and interests?
- How satisfied are you with your physical condition?
- In general, how satisfied are you with the renal transplantation?

APPENDIX B

Set of Questions on Physical Complaints

Respondents were asked to rate each item on a scale of 1 to 4, with 1 = not at all and 4 = very much.

Regarding the past week,

- did you have a need for rest?
- were you feeling sick?
- were you feeling weak?
- did you feel tired?
- were you feeling physically well?
- did you have trouble with falling asleep?
- did you have problems to sleep on?
- did you have loss of appetite?
- did you suffer from nausea?
- did you have to vomit?
- did you consider yourself too fat?

Regarding the past week, did you suffer from:

- stiff, tender, or painful muscles?
- a swollen face?
- abdominal pain?
- diarrhea?
- constipation?
- dizziness, feeling faint?
- loss of sight?
- a skin disorder?
- shortness of breath?
- headache?
- swollen ankles?
- burning eyes?
- stomachache?
- heartburn?
- excessive appetite?
- trembling hands?
- bruises?
- a tingling feeling in hands or fingers?
- excessive hair growth?

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NORMALIZATION OF CIRCADIAN BLOOD PRESSURE PROFILES AFTER RENAL TRANSPLANTATION

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Most patients with secondary hypertension due to renal disease or on maintenance hemodialysis have lost the physiologic fall of blood pressure during sleep. To test the notion that kidney transplantation normalizes the blood pressure profile, we monitored ambulatory blood pressure over 24 hr in 45 patients (29 males and 16 females) after successful renal transplantation.

The longer the time after renal transplantation, the more marked was the decrease of blood pressure during sleep (r=0.38, P<0.01). This effect of time after renal transplantation on the fall of blood pressure during sleep was independent of the prevailing level of 24-hr ambulatory blood pressure. The prevalence of dippers (defined by a fall in mean blood pressure during sleep of 10% or more of the awake mean) increased from 27% in the early phase (< 7 months) to 73% in the late phase (≥ 1 year) after renal transplantation (P<0.01). Again, this effect was not attributable to the level of 24-hr ambulatory blood pressure and concomitant antihypertensive or immunosuppressive medication.

We conclude that renal transplantation leads to a normalization of the circadian blood pressure profile with a marked decrease of blood pressure during sleep. As a consequence, the lower hemodynamic load imposed on the cardiovascular system may in turn lead to a reduction of cardiovascular morbidity and mortality.

In normotensive subjects as well as in patients with mild to moderate essential hypertension, blood pressure (BP)* falls by 15–25% during sleep (the "dipper" pattern) (*1*, *2*). In contrast, in patients with secondary hypertension, this decrease

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* Abbreviations: BP, blood pressure; MAP, mean arterial pressure; RT, renal transplantation.